57 Sleep

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57.1 Introduction: What Is Sleep?

Even unicellular animals display circadian modulations in their activity and responsiveness. However, the term "sleep" is used to describe the periods of reduced activity in "higher" animals. For a state to qualify as sleep, three criteria must be met.

- Motor changes. Movements are reduced or become more stereotyped. In some animals, a characteristic sleep posture is assumed. There may be more than one sleep posture, with each posture correlated with a particular stage of sleep. For example, in certain species sleep posture differs in REM and non-REM sleep (see below). Most animals are immobile during sleep, but some, such as marine animals, need to move while they sleep.
- Sensory changes. Animals act to minimize sensory input during sleep. The eyes are typically closed. Sleep postures and locations are chosen to minimize somatic and auditory stimulation. Responsiveness to applied sensory stimuli is reduced as a result of changes in functioning of brain synapses.
- Rapid reversibility. To confirm sleep, as distinct from coma, hibernation and estivation, it must be demonstrated that the animal can be rapidly awakened. Under these conditions, sensory and motor activity revert to those of waking.

57.2 Brain Activity in Sleep

Certain patterns of brain wave activity accompany sleep states. Berger [7] first described the high-voltage waves that appeared on the scalp electroencephalograph (EEG) during sleep, in contrast to the lower voltage patterns apparent during waking. This somewhat paradoxical state of affairs can be understood by appreciating that synchronized activity of excitatory and inhibitory postsynaptic potentials in adjacent cortical neurons will produce summated high-voltage potentials. Asynchronous patterns of activity in adjacent neurons tend to cancel each other, producing low voltages. Therefore, the higher voltages recorded in sleep are not a sign that more information processing is going on in the brain, but only that adjacent neurons are "idling" in synchrony.

It took nearly 25 years from the discovery of high-voltage slow waves in the EEG during sleep by Berger to the finding that during certain periods of sleep, low-voltage EEG signals occur. These low-voltage EEG signals are virtually indistinguishable from those of waking. They are accompanied by rapid eye movements and other phenomena [4], which gave rise to the current nomenclature for that component of sleep, i.e., rapid eye movement (REM) sleep.

57.2.1 Non-REM Sleep

REM sleep and non-REM sleep, while sharing the three criteria of sleep enumerated above, differ in subtle and not so subtle ways. In humans, non-REM sleep can be subdivided into four distinct stages (Fig. 57.1). These stages are defined by EEG criteria [77]. The high-voltage waves of non-REM sleep consist of relatively high-frequency waves, in the 8-12 cycle range, and low-frequency waves, in the 0-4 Hz range. The 8-12 Hz waves occur in bursts; they start at

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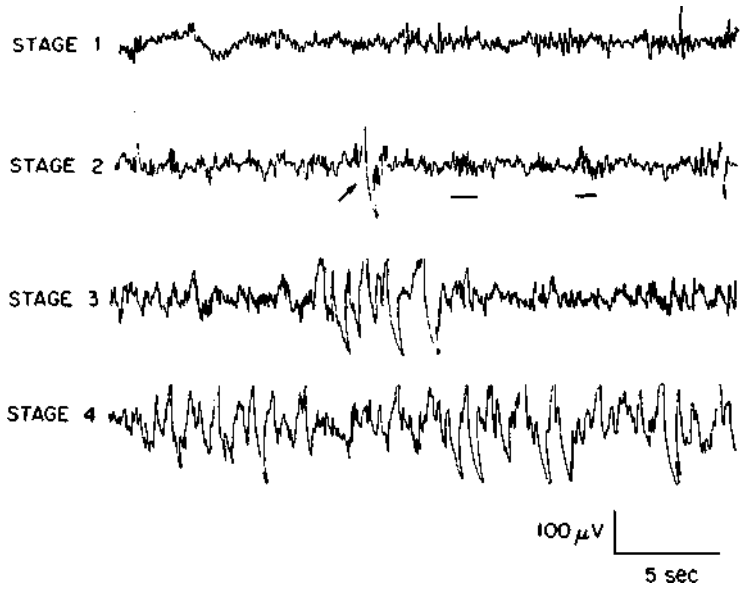

Fig. 57.1. Stages of non-REM sleep in the human. In humans, non-REM sleep can be subdivided into four distinct stages. In stage 1 sleep, the rhythmic 8 Hz activity of relaxed waking is replaced by the low-voltage mixed pattern of stage 1 sleep. Stage 2 sleep is defined by the presence of large waves called K complexes (indicated by the *arrow)* and regular waxing and waning bursts of 8-12 Hz activity called sleep spindles (indicated by the *two underlines).* As a person goes from stage 1 to stage 4, the amplitude of the EEG and the proportion of time filled by slow (low-frequency) waves increases. (Reprinted with permission from [11])

a low amplitude, and over an interval of a second or less reach their maximum amplitude, falling back to baseline at the same speed. These waxing-waning patterns of EEG activity have been termed "spindle" activity, because of the resemblance of the overall waveform to the spindles used in sewing mills. The four stages of human non-REM sleep form a continuum, stages 1-4 having an increasing proportion of slow wave activity and a decreasing proportion of spindle activity. Stage 4, consisting largely of slow waves, is often considered the stage of deepest sleep. In stage 4, arousal thresholds are highest and mental activity is lowest. Total sleep deprivation in humans produces a relative increase in the proportion of stage 4 sleep when the subject is allowed to sleep again [9], indicating that it may be the most efficient stage for fulfilling sleep need. Adults [18,22] and infants after the first month of life [88], show more high-amplitude slow waves at the beginning of the night than in non-REM periods as the night progresses; the decline in the proportion of slow waves suggests a "restorative" process is under way during non-REM sleep and that large, low-frequency slow waves are indicative of that process [22]. This interpretation is supported by evidence that the proportion of slow waves generated during a midday nap are missing in the first non-REM period of the subsequent night-time sleep [24]. In animals, sleep can be subdivided according to similar EEG criteria to those used in humans, but subdivisions of non-REM sleep are typically less well differentiated. Many popular sleep schemes for scoring sleep in the cat and rat subdivide non-REM sleep into just two stages, with the "deeper" stage having a higher proportion of slow waves [111].

57.2.2 REM Sleep

REM sleep is generally not subdivided into stages in the same fashion as non-REM sleep; however, periods of intense phasic twitching activity are distinguished from quieter periods within that state. Normally, REM sleep does not occur at sleep onset; rather, it follows an episode of non-REM sleep. REM sleep and non-REM sleep alternate throughout the sleep period. The non-REM-REM cycle lasts about 90 min in the human and less in smaller animals (approximately 30min in the cat). The EEG during REM sleep is very similar to the waking EEG, although mathematical techniques, such as spectral analysis, can reveal subtle differences. In animals, a remarkable EEG potential has been observed during the sleep cycle, the PGO spike (Fig. 57.2). The abbreviation "PGO" stands for pontine, geniculate, occipital. The term derives from the order of latency of spike appearance in simultaneous recordings from these areas, with the waves appearing first in the pons, then propagating to the geniculate and then to the occipital cortex [51,95]. The initial appearance of the high-voltage PGO waves precedes REM sleep onset by 60s or more. As REM sleep approaches, the amplitude of **these** waves is somewhat reduced and the frequency is **increased,** with bursts of waves occurring during REM **sleep. PGO** spikes appear to be one of several neural events linked to

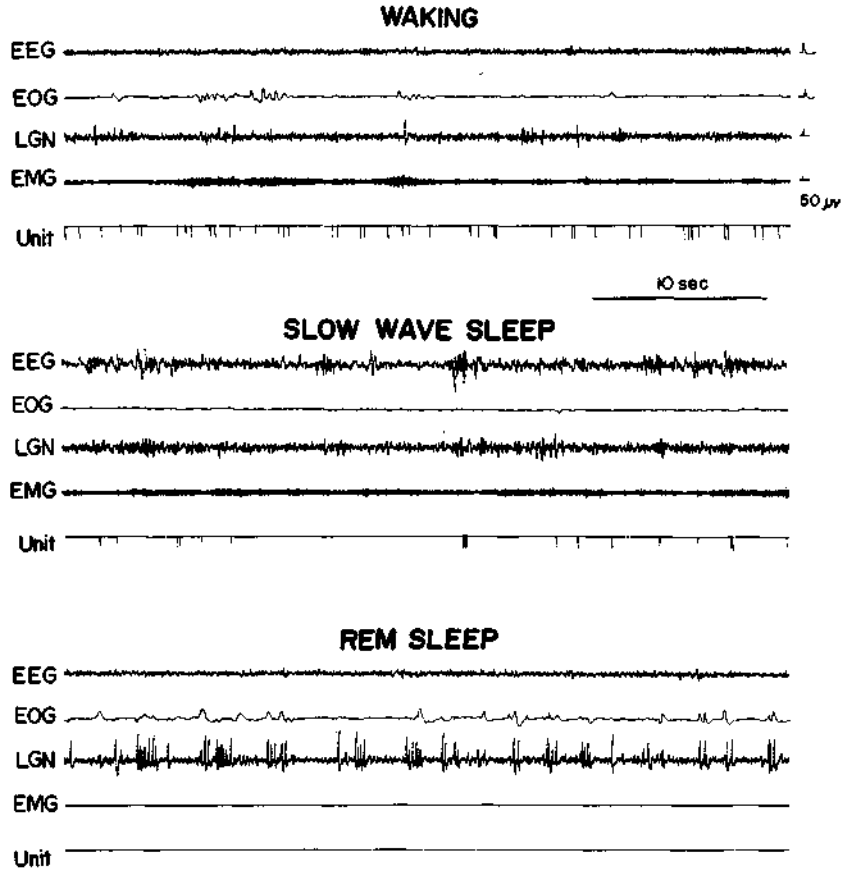

Fig. 57.2. The sleep cycle in the cat. The EEG during REM sleep looks very much like the waking EEG, although spectral analysis techniques can reveal fairly subtle differences. In animals, a very striking EEG potential has been observed during the sleep cycle. This is the PGO spike which can be recorded in the pons (P) in the brainstem, lateral geniculate (G) nucleus of the visual pathway and the occipital (O)cortex. The PGO spike is believed to be related to the visual imagery of dreams. Here the PGO spikes are visible on the channel marked *LGN* (lateral geniculate nucleus). PGO spikes occur most frequently during REM sleep. The *Unit* displayed in this figure is the pulse output from a "window discriminator" of a recording from a "REM sleep-off" cell, which is tonically active during waking and inactive during REM sleep. *EEG,* cortical EEG; *EOG,* electrical recording of eye movements; *EMG,* recording of neck muscle tone

waves of excitation that sweep through the brainstem and are propagated to the forebrain and to the spinal cord during REM sleep. PGO waves do not appear to be the trigger for this excitation, since the spikes may precede or follow twitches of the neck and middle ear musculature [74,119].

REM sleep is the only naturally occurring state in which most or all of the muscle tone in "antigravity" muscles is abolished [50] by hyperpolarization of motoneurons [12]. This suppression of muscle tone prevents the contraction of muscles during REM sleep, even though brain motor systems are intensely active, and as we will see, it has profound implications for clinical aspects of sleep, such as obstructive sleep apnea, narcolepsy and REM sleep behavior disorder.

The discovery of REM sleep [4] was quickly followed by the discovery that individuals awakened during this state invariably reported that they were dreaming [17]. Further work has shown that while dreams are more common and vivid in REM sleep, non-REM sleep is not devoid of mental activity, with non-REM-sleep dreams tending to be more thought-like and less action filled [28].

57.3 Respiratory Activity

Sleep states exert a profound influence on respiratory patterns. It is worth noting that the respiratory musculature includes the diaphragm, as well as a large number of other muscles that serve multiple functions in addition to assisting air movement associated with breathing. These muscles include the thoracic and abdominal wall muscles, muscles which elevate the rib cage, muscles serving to dilate the upper airway of the pharynx and larynx, and the tongue muscles, which enlarge the oral airway with each breath [86]. Since respiratory musculature and other skeletal musculature share similar innervation, the suppres-

sion of muscle tone occurring in REM sleep similarly extends to most respiratory musculature and "paralyzes" them or greatly reduces their action, except for the diaphragm. The diaphragm, although altering activation patterns during REM sleep, largely maintains respiratory movements during that state [94]. The diaphragm in animals is often subject to transient inhibition during REM phasic periods [71]. The routine paralysis or reduction in tone of large numbers of accessory respiratory muscles with every episode of REM sleep obviously has major implications for disordered breathing. REM sleep, in addition to inactivating most non-diaphragmatic musculature, induces an increase in the rate and the variability of breathing, with especially rapid rates occurring with phasic events of that state. Non-REM sleep, on the other hand, induces breathing patterns of extreme regularity and slowed rates; inspiratory times are especially prolonged. Tone of accessory respiratory muscles is normally maintained during non-REM sleep, unlike the REM state. Arousal to respiratory stimuli, such as hypercapnia or hypoxia, or to irritating airway stimuli that would otherwise induce cough, is delayed in REM sleep [107]; the latter characteristic may be of importance in understanding how infants may not arouse from a life-threatening challenge in the sudden infant death syndrome.

Evaluating the responsivity to CO_2 and O_2 during sleep is complicated by phasic activation of multiple sources of neural drive to breathing during REM sleep, which makes interpretation of ventilatory challenges difficult. Two aspects of responsivity are important: the change in breathing pattern with CO_2 or O_2 challenge, and thresholds for arousal when extremes of either chemical challenge are presented. It appears that the ventilatory response to hypercapnia is somewhat diminished during non-REM sleep and that the response during REM sleep is difficult to interpret; similarity of the response during REM, compared with waking states, depends heavily on whether the challenge is delivered during tonic or phasic periods of the state. Hyperoxia depresses breathing during non-REM sleep in infants and has variable effects during REM, suggesting that brainstem mechanisms controlling the highly variable respiratory patterning during that state can override such ventilatory challenges. Arousal thresholds to hypercarbia are raised in REM sleep [105]. The marked influence of sleep state on respiratory patterning has led to use of breathing characteristics as a useful indicator for automatic classification of state, particularly in cases where EEG measurements are difficult or costly to obtain [39], e.g., when infants are being monitored in the home environment.

57.4 Autonomic Activity

Autonomic nervous system activity is dramatically influenced by sleep states concomitant with changes in other components of the nervous system. A principal manifestation of parasympathetic nervous system action is reflected in effects on the cardiovascular system. Heart rate slows during non-REM sleep. Normally, heart rate increases and decreases with the respiratory cycle, a variation called "respiratory sinus arrhythmia"; the extent of this respiration-related variation in rate increases in non-REM sleep [39]. Longer term variation in heart rate is usually absent during non-REM sleep, perhaps because phasic movements are greatly reduced during that state, and baroreceptor and other responses to movement are thus minimal. Slower modulation of the respiration-induced modulation, however, is found during non-REM sleep, and possibly results from thermal and slow circulation sources. During REM sleep, respiration-induced sources of variation are intermixed with very large and sustained increases and decreases in heart rate; enhanced variation is especially prominent with the phasic phenomena of REM sleep. The nature of sleep-related cardiac rate variation is of clinical interest, since scatter plots of one cardiac interval against the next are exceptionally useful in describing trends in congestive heart failure [118] and in infants at risk for the sudden infant death syndrome [87]. In REM sleep, tonic sympathetic tone in the cervical sympathetic ganglion is minimal [6,81], although phasic sympathetic activity may appear in conjunction with the twitching and PGO activity seen in this state [46]. This lack of sympathetic tone in REM sleep is in striking contrast to the situation during waking, a state in which sympathetic activity levels are maximal. The pupils of the eye are smaller in REM sleep than in any other state, reflecting the absence of tonic sympathetic activity [115]. Regional differences appear in sympathetic tone in animals; while cat mesenteric and renal vessels dilate, the external iliac artery constricts. The sympathetic enhancement to the lower limbs may be mediated by locally organized reflexes [59]. In males, a striking correlate of autonomic activity during REM sleep is the presence of penile erections [26]. Thermoregulation also varies as a function of sleep state. Body temperature falls during non-REM sleep. However, this fall is regulated, and the body responds to changes in the ambient temperature with compensatory changes in heat loss and production. In contrast, in REM sleep thermoregulation is greatly reduced [73]. Body temperature tends to drift towards environmental temperature. In this sense, animals become poikilothermic or "cold blooded" during REM sleep. When body temperature changes become too extreme, the animal reduces the duration of REM sleep.

57.5 Endocrine Activity

Sleep is a powerful modulator of endocrine activity. The blood level of a number of endocrine hormones is correlated with sleep states. Sleep deprivation studies and studies in which sleep is shifted with respect to the circadian cycle have allowed identification of the hormones that are released in particular sleep stages in humans. Growth hor-

mone is linked to stage 4 non-REM sleep. Prolactin release is also linked to sleep, with maximal levels reached in the morning. Thyroid-stimulating hormone has its peak release during the evening and declines during the sleep period. In children approaching puberty, the release of luteinizing and follicle-stimulating hormone occurs at sleep onset and is inhibited during waking. A circadian rhythm of cortisol release persists even during total sleep deprivation. However, when sleep is allowed to occur, the level of cortisol release is reduced below the level dictated by the circadian cycle. Melatonih release, while normally highest during the night, is not linked to sleep, but is sensitive to changes in the light-dark cycle that entrain the circadian rhythm [66,112,117].

57.6 Brain Activity

Changes in physiological function during sleep are driven by variations in neural activity. In most brain areas, neural discharge is highest during waking motor activity [95]. guidance of movement. In contrast, non-REM sleep is associated with changes in these neural patterns. In the thalamus and cerebral cortex, the unpatterned neuronal discharges characterizing normal information processing in waking are replaced by the short, high-frequency neuronal bursts followed by long pauses. This idling pattern accompanies the high-voltage slow waves found in this state [102]. Adjacent neurons tend to fire their bursts at the same time. It is this synchronization, rather than a reduction in rate, that characterizes neural discharge in the cortex and thalamus during non-REM sleep. However, a small reduction in rate in non-REM sleep has been reported in most cortical areas. In the brainstem, the overall rate of neuronal discharge drops dramatically in non-REM sleep, with many neurons becoming quiescent. During REM sleep, neural activity in most brain areas is more similar to the pattern of waking than of non-REM sleep (Fig. 57.3). Intense burst discharge is interspersed with periods of silence, as in waking. In the brainstem, where the most extensive observations of neuronal activity have been made, discharge rates in REM sleep typically equal or exceed maximal rates in waking. This is particularly true of cells that are active during waking movements.

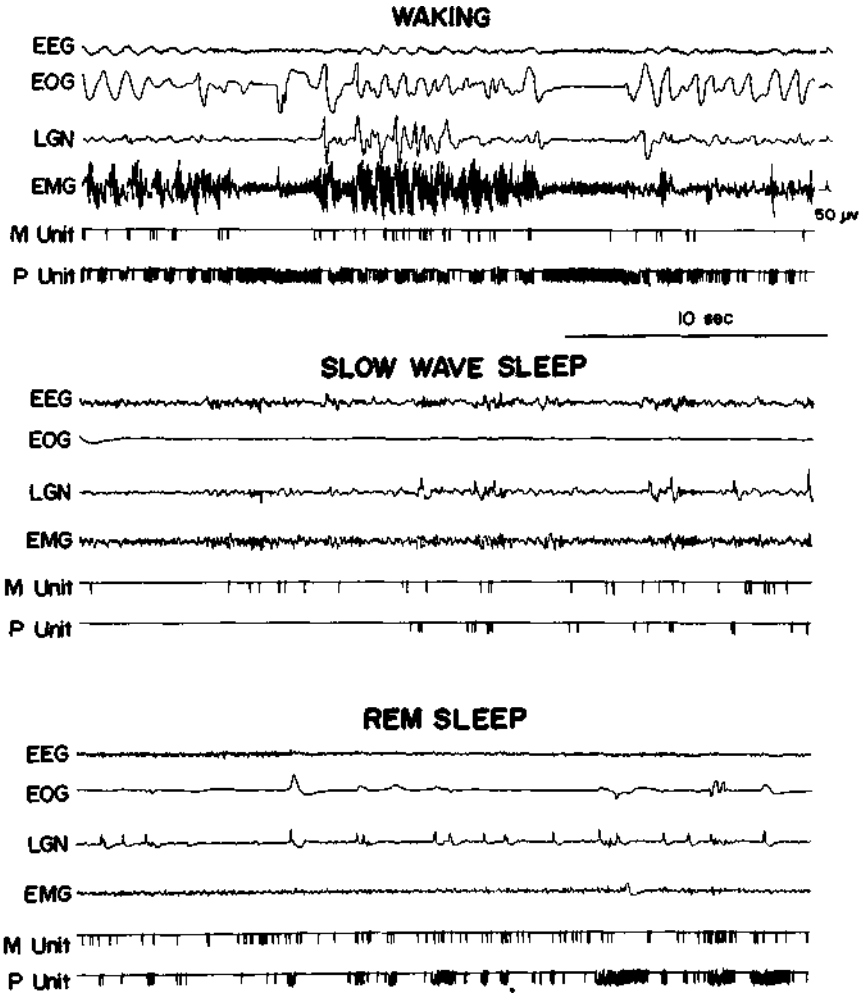

Fig. 57.3. Neural activity in most brain areas in REM sleep is more similar to the pattern of waking than of non-REM sleep. This figure shows a simultaneous recording of a unit in the medial medulla of the brainstem (M *Unit)* and of a unit in the medial pons of the brainstem *(P Unit)*. Note the activation of both units during both waking and REM sleep

In contrast, most brain cells have their lowest discharge rates in non-REM sleep.

57.7 Developmental Changes

In all animals examined to date, sleep duration is maximal at birth or prenatally [20,36,84]. REM sleep occupies the highest percentage of sleep time in young animals, gradually decreasing and then reaching a constant level by the end of young adulthood. The intensity of motor activity in REM sleep is also greatest in infancy. Changes in non-REM sleep also occur with age. Slow waves in the human sleep EEG diminish, so that stage 4 does not occur frequently or for extended periods beyond the age of 30 [21].

57.8 Sleep in Animals

Sleep-like states can be observed throughout the animal kingdom. For example, honey bees have a circadian rhythm of motor activity [53]. Sensory responsiveness is reduced during periods of inactivity; moreover, these states of reduced responsiveness are rapidly reversible, meeting the major defining characteristics of sleep. Sleep-like periods of reduced motor activity and sensory unresponsiveness have been described in reptiles and fish [27,110]. Some evidence of sleep debt after sleep deprivation has also been reported in these species. While these states have the immobility, periodicity and elevated sensory response thresholds of mammalian sleep, the brain wave signs of sleep differ from those in mammals. For example, in reptiles the EEG (this is recorded from forebrain structures, which are more closely related to the basal ganglia than to the cerebral cortex) pattern is high voltage in waking and low voltage in sleep, i.e., the opposite of the mammalian pattern.

In birds, an unusual pattern of sleep has been described. Some birds appear to be able to have non-REM sleep periods in one cerebral hemisphere at a time [3]. Typically, the contralateral eye is closed while each hemisphere sleeps. One can speculate that this pattern allows a level of "hemivigilance" that has survival value. In other birds, both hemispheres sleep simultaneously. Birds clearly have a REM sleep state, which is always expressed bilaterally. REM sleep durations are relatively short, lasting as little as 2 s at a time in some species. There is no clear evidence for the existence of REM sleep in reptiles, although there have been some reports of phasic activity during sleep [5,47]. With two exceptions (discussed below), all mammals have both REM and non-REM sleep. The amounts of sleep range from 19.4 h a day in the thick-tailed opossum to 1.9 h in the giraffe [120]. In general, larger animals sleep less; one hypothesis explaining this relationship is that larger animals have lower metabolic rates and therefore have less need of the small energy conservation benefits of sleep. However, partial correlations of metabolic rate with sleep time (mathematically holding body weight constant) indicate that sleep time correlates negatively with metabolic rate. Therefore, while body size is a powerful predictor of sleep time, the underlying physiological mechanism responsible for this relationship remains unclear. REM sleep time correlates with non-REM sleep time; animals that spend a large percentage of the day asleep have large amounts of REM sleep. The strongest correlate of REM sleep time is the relative immaturity of animals at birth [52,120]. Immature animals have large amounts of REM sleep after birth. Such animals also show relatively large amounts of REM sleep when they reach adulthood, compared with animals that are mature at birth. One hypothesized function for REM sleep is that it provides stimulation that facilitates neural development [84]. This hypothesis does not address the question of why adult animals should continue to have REM sleep. Because of the association of REM sleep with dreaming and dreaming's association with creative processes, many have speculated that REM sleep serves some higher cognitive function across the animal kingdom. However, phylogenetic studies do not show that humans have uniquely large amounts or percentages of REM sleep. Humans are in the middle of the animal kingdom on most measures of REM sleep time [1]. Our REM sleep time per day is less than one-third that of the thick-tailed opossum. We devote 24% of our sleep time to REM sleep, while the armadillo devotes 34% of its sleep time to REM sleep [120].

The two mammals that have been reported to lack REM sleep are the dolphin and the echidna. The dolphin has uni-hemispheric non-REM sleep analogous to that seen in birds. The two hemispheres never "sleep" at the same time, according to EEG criteria [68,69]. No periods of EEG desynchrony, with the immobility and rapid eye movements that characterize REM sleep in other mammals, have been found. However, depth electrodes were not implanted in these animals, which were studied in a relatively unnatural environment in which their range of movement was relatively limited. Furthermore, the closely related cetacean, the pilot whale, has been reported to have small amounts of REM sleep [93], suggesting that REM sleep may have been missed in the dolphin.

The short-nosed echidna is a primitive mammal native to Australia. It is an anteater and has prominent spines resembling the quills of the porcupine. It belongs to the order called monotremes. The only other members of the monotreme order are the long-nosed echidna and the duck-billed platypus. These last two species have not had their sleep studied. Monotremes lay eggs, like reptiles. They have a low body temperature, but are homeotherms. They lack nipples, but they do nurse their young, by secreting milk from their ventral surface. They have hair, like other mammals. The mouth of the echidna does not have well-defined teeth, but rather has both avian and mammalian features. Fossil evidence demonstrates that there has been little change in the structure of monotremes since their evolution over 75 million years ago [34]. Thus, living monotremes resemble the animals that were present at the

time of the initial appearance of the mammalian line. Thorough, long-term, studies of the echidna have shown that they do not have REM sleep, as judged by either surface or depth electrodes [2]. Evoked response indicators of behavioral state, using the cortical response to electrical stimulation of subcortical structures, also indicate that the echidna lacks a REM sleep state. The primitiveness of the echidna, combined with its lack of REM sleep, suggests that REM sleep first appeared after the evolution of the mammalian line. However, the unequivocal presence of REM sleep in birds indicates that the common reptilian ancestors of birds and mammals must have had either REM sleep or a state similar enough to REM sleep to allow the state to "evolve" in both.

57.9 Sleep Deprivation

Total sleep deprivation studies have been used to shed light on the function of sleep. Human studies performed for up to 10 days show remarkably few behavioral or physiological deficits in subjects. Body temperature tends to fall somewhat during the period of deprivation. A consistent finding is the presence of short "microsleeps," periods of reduced alertness. These microsleeps are accompanied by EEG "spindles," an EEG sign normally present in non-REM sleep. Thus, the primary symptom of sleep deprivation in humans appears to be the intrusion of sleep into waking [45].

Recent sleep deprivation studies in rats have taken advantage of computer technology to achieve relatively complete sleep deprivation for extended time periods. Animals were deprived by being forced to move to avoid contact with water whenever the brain activity of sleep occurred. Control rats were forced to move in the same way, except that the stimulus was not contingent on their sleep patterns. Therefore their sleep was much less disturbed. This complete sleep deprivation produces death in rats within 10-32 days, while there are few ill effects in the controls [79]. Death is preceded by the development of lesions on the rats' tails and paws and weight loss despite increased food intake. Total sleep deprivation produced an initial increase in body temperature followed by hypothermia in the final quarter of the deprivation period. Selective deprivation of REM sleep or deprivation only of deep periods of non-REM sleep (identified by high-voltage EEG activity) produced similar symptoms, with death occurring over a somewhat longer time period. The underlying cause of death is unclear. Immune dysfunction has been implicated in the final stages, but this may be a result of the debilitation, rather than its cause. It is also unclear why sleep deprivation is lethal in rats while deprivation in humans, albeit of shorter duration, does not appear to have such drastic effects; perhaps the higher metabolic rate in rats underlies the difference.

Selective deprivation of REM sleep produces a rebound in the amount of REM sleep, indicating a specific need for this kind of sleep [16]. After REM sleep suppression, recovery REM sleep is more "intense" with more frequent twitches and eye movements. REM sleep suppression by barbiturates or by alcohol abuse is followed by a similar rebound of REM sleep. Sleep apnea, which interrupts sleep and thereby suppresses REM and deep non-REM sleep, produces a marked REM sleep rebound when the airway is restored by mechanical means [106); (see also below). REM sleep deprivation also reduces seizure thresholds [13]. Some work has indicated that REM sleep deprivation interferes with memory consolidation. However, other work has disputed this conclusion, finding little evidence for a major role of REM sleep in learning [30,100,113]. It is likely that any REM sleep role in learning is relatively minor.

57.10 Sleep Generation Mechanisms

Under normal conditions, REM sleep and non-REM sleep are linked in a regular alternation. In the adult animal, non-REM sleep always precedes REM sleep. While damage to the nervous system will invariably affect both stages of sleep, investigations of sleep mechanisms have identified regions of the nervous system that appear to be linked to either REM or non-REM sleep.

57.10.1 Non-REM Sleep

Recent work has focused on diencephalic mechanisms generating non-REM sleep states. Hypothalamic and adjacent basal forebrain regions appear to regulate the duration and timing of non-REM sleep, while thalamic mechanisms, interacting with mesopontine (midbrain and pontine) and cortical regions, generate the EEG changes characteristic of non-REM sleep.

Damage to the basal forebrain produces profound insomnia [108], with loss of both non-REM and REM sleep. This has been demonstrated after basal forebrain damage in humans and after experimentally placed lesions in animals. Conversely, stimulation of this region with electrical pulses produces a short latency onset of sleep [104]. When neuronal activity was recorded in the basal forebrain, a distinct cell type was discovered. This cell type was selectively active in non-REM sleep, with little activity in either waking or REM sleep [64,65,109]. Some cells in this area are activated by heat, suggesting that they may mediate the somnogenic effect of heat, such as the sleep produced by a day at the beach or by a hot bath. Cells in the posterior hypothalamic region may also participate in the control of sleep by facilitation of waking. Inactivation of this region produces extended sleep periods.

The high voltage EEG changes characteristic of non-REM sleep have been shown to be the result of an interplay between the thalamus, mesopontine region and the cerebral cortex [102]. The nucleus reticularis of the thalamus is capable of generating discharge frequencies characteristic of sleep spindles. This is an intrinsic rhythm, since the nucleus reticularis can generate it even when its connec-

tions with the other regions of the thalamus are severed [103]. The nucleus reticularis is able to synchronize the activity in thalamic projection nuclei, which produce the cortical changes recorded as sleep spindles. The nucleus reticularis is under the control of cholinergic cells in the mesopontine region [specifically the latero-dorsal tegmental (LDT) and pedunculopontine (PPN) nuclei of the pons]. Acetylcholine release from the axon terminals of these cells hyperpolarizes cells in nucleus reticularis, thereby blocking at the cellular level the ionic mechanisms responsible for spindle generation [102]. At least some LDT-PPN cells are active in waking and REM sleep, at times when sleep spindles are blocked. These cells may well serve as a link between the pontine mechanism controlling REM sleep and the thalamic mechanism controlling non-REM sleep.

57.10.2 REM Sleep

While diencephalic mechanisms are of primary importance in the generation of non-REM sleep, brainstem mechanisms appear to be essential to REM sleep. Jouvet [50] first demonstrated that the decerebrate cat (i.e., with all brain tissue rostral to the midbrain removed) showed all of the signs of periodic occurrence of REM sleep in the brainstem. These brainstem signs of REM sleep included the regular recurrence of periods of rapid eye movements, accompanied by loss of neck muscle tone, pupil meiosis (constriction) and pontine slow wave "spikes" or high-voltage potentials, the earliest component of the PGO spike. Work in our laboratory has shown that none of these signs are present in body regions connected to the medulla and spinal cord after transection at the ponto-medullary junction [97]. However, we found that after transections of the brainstem at the ponto-medullary junction, several of the forebrain signs of REM sleep, including PGO spikes and EEG desynchrony, were present in the rostral half of the brain [96]. This work indicates that when the pons is connected to the medulla, REM sleep signs appear in the caudal portion of the brain. When the pons is connected to the forebrain, REM sleep signs appear in the forebrain. Further studies have been performed on the pontine region (actually the pons and caudal portion of the midbrain), which is implicated in the transection studies. In the otherwise intact animal, extensive damage to the pons, particularly the region termed the nucleus reticularis pontis oralis (a nucleus occupying much of the rostral pons), reduces or completely prevents REM sleep. The extent of REM sleep loss is proportional to the percentage of pontine cholinergic cells lost [116]. Stimulation of points in the dorsal and ventral nucleus reticularis pontis oralis with the acetylcholine agonist carbachol, or with acetylcholine itself produces REM sleep signs [29,54]. This effect is dramatic and immediate, with injection in the waking animal producing a loss of muscle tone, PGO spikes or REM sleep itself within 60s [114].

The pontine region implicated in REM sleep control by the above stimulation and lesion studies contains .neurons whose activity is consistent with their mediating these effects. Most cells in the brainstem have increased activity in active waking and REM sleep, proportional to their activity in non-REM sleep. Such cells are also in the majority in the pons [95]. In the waking states, these cells discharge in relation to motor activity, including eye and head movements. In REM sleep, their discharge produces the activation of these same motor systems, although the expression of skeletal motor activity is blocked by an active inhibitory circuit producing hyperpolarization of the motoneurons. In particularly active periods of REM sleep, the phasic activity can overcome the motoneuron inhibition, producing twitches. Many of the cholinergic pontine cells are of the REM-waking-active type and have ascending projections. These projections cause the EEG desynchrony of waking and REM sleep through their inputs to the nucleus reticularis of the thalamus [72].

In addition to these "REM sleep-waking-on cells," the pons and adjacent brainstem regions also contain "REM sleep-on" and "REM sleep-off" cells. REM sleep-on cells are either silent or have low levels of activity in waking [85,92,98]. Often, in contrast to motor-related cells, they will decrease discharge in active waking relative to their quiet waking discharge rate [98]. They remain inactive in non-REM sleep. These cells have their maximal discharge rates in REM sleep. The transmitter released by these cells is unclear. While some may be cholinergic, most are not [92,98]. Pontine glutamatergic and peptidergic mechanisms have been implicated in atonia control [55-57]. Some REM-on cells have a role in triggering the motor atonia of REM sleep. Other REM-on cell types may control other aspects of REM sleep.

REM sleep-off cells are also located in the pons (Fig. 57.2, unit). These cells have tonic activity in waking and decreased activity in non-REM sleep, and are silent in REM sleep [43,62,63]. The best current evidence indicates that all noradrenergic cells in the locus coeruleus and adjacent regions are of this type [95]. These cells may be involved in the reduction of sympathetic activity that is linked to REM sleep. Through the widely ramifying projections of the noradrenergic locus coeruleus cells to cerebral and cerebellar cortex, the cessation of discharge must have a major effect on signal processing in REM sleep. Norepinephrine is thought to increase the "signal-to-noise" ratio of neuronal function. Thus, this cessation of discharge may contribute to the peculiar mentation of REM sleep and the inability to recall most dreams. Lesions restricted to the noradrenergic cells do not greatly disrupt REM sleep [49], indicating that they are not directly involved in REM sleep control. However, extensive evidence shows that noradrenergic cells do modulate REM sleep duration [48].

A second group of REM sleep-off-cells appears to be identical to the serotonergic cells of the midline raphe nuclei [62]. It is apparent that at least some of these cells are directly involved in "gating" the occurrence of PGO spikes through synapses on cholinergic pontine cells [58]. Thus, the cessation of activity in these cells immediately prior to and during REM sleep causes bursting activity in

cholinergic cells in the pons. These bursts propagate rostrally to the thalamus. PGO spikes are one of several phasic sensorimotor phenomena that characterize REM sleep [119]. The substrate of the other phasic motor phenomena of REM sleep has not been identified.

57.10.3 Visualization of Structural Activation During Sleep

By far the largest source of data on neural mechanisms mediating sleep derives from electrophysiological tools of macro- and micro-electrode recording. Data on subcortical functions during sleep states obviously derive principally from animal studies using such electrode procedures. Recent technological advances, however, allow visualization of functional activity of both surface and deep structures; in some cases, the visualization can be performed non-invasively on human subjects. Sleep researchers quickly incorporated positron emission tomography (PET; cf. Chaps. 28, 29) techniques into their range of tools for determining activation of structures during particular states. PET visualization techniques, however, suffer from severe spatial and temporal resolution constraints. The technique typically involves assessment of usage of radiolabelled glucose by cellular elements over a defined period of time, and that time resolution is frequently measured in tens of minutes. Since neural structures undergo dynamic changes within states much more rapidly, determination of changes in brain structures has been difficult, especially for separating phasic and tonic aspects of REM sleep. Moreover, the severe spatial resolution (tens of millimeters) further complicates the efforts of these researchers. Nevertheless, PET procedures allow identification of particular neurotransmitter actions and provide exceptionally valuable insights into neural processing during normal and abnormal activation. PET procedures in the human show that an overall decline in metabolic activity accompanies non-REM sleep, with a greater decline in frontal than temporal or occipital regions, and a greater decrease in basal ganglia and thalamic sites than in cortical areas. Metabolic activity increases during REM sleep in a heterogenous fashion, and especially in cingulate cortex. Asymmetries in metabolic activity develop in basal ganglia areas during REM, but not non-REM, sleep. Animal studies confirm the findings of diminished metabolism over cortical and thalamic areas during non-REM sleep and a more regionalized activation in REM, especially in motor and limbic (especially hippocampal) regions [10,60,76]

At the time of writing, investigators are just beginning to examine aspects of brain activity during states with functional magnetic resonance imaging (fMRI) techniques [33]. The fMRI procedure is based on detection of differences in magnetic susceptibilities induced by physiological dynamics accompanying neural activation. These inhomogeneities may be induced by increased blood flow or volume with accentuated neural discharge and the relative proportion of oxyhemoglobin and deoxyhemoglobin accompanying these vascular changes during increased discharge. Oxyhemoglobin and deoxyhemoglobin exhibit different magnetic susceptibilities and thus elicit different intensities of MR signal. Other, as yet undescribed, fluid dynamics may mediate other detectable magnetic properties. The procedures have been used to visualize noninvasive dynamic activation of visual and somatic sensory pathways in humans, and should be exceptionally useful for the description of activation of neural structures during sleep. The temporal and spatial resolution of this technique are rapidly improving to the point that sub-second acquisition of images with visualization of <2 mm resolution can be readily attained.

Optical imaging techniques allow visualization of neural activity over wide areas in subcortical and cortical areas of animals at very high temporal and spatial resolution. Voltage- or calcium-sensitive dyes have been used to illustrate properties of cells within in vitro slice preparations; however, it has now become apparent that a variety of physical membrane and ionic changes accompany cell discharge, and that these changes alter the scatter of illuminating light which can be assessed in in vivo preparations; the nature of the transmission or scatter is, of course, dependent on light wavelength. Scattered light can be captured by a charge-coupled diode (CCD) camera, or can be transmitted through a coherent optic fiber bundle to a CCD that retains spatial information [19,33,80]. Thus, activation and inactivation of neural elements from several thousand neurons can be observed simultaneously, and aspects of neural interaction, such as columnar organization, can easily be visualized. Using such procedures, Poe et al. [75] demonstrated relative activation of dorsal hippocampal structures in non-REM sleep over quiet waking, and an even further activation during REM sleep over non-REM and waking states (Fig. 57.4). Localized neocortical sites did not show such an activation during REM. The technique promises to assist examination of the organization of neural elements within structures involved in state-related functions, and will complement optical transmission studies pioneered by Hayaishi and his group [41,70].

57.11 Sleep Pathologies

Sleep disorders medicine is one of the most rapidly expanding medical specialties. This expansion is the result of the appreciation of the enormous morbidity associated with sleep-related diseases and the effectiveness of some recent treatments for sleep problems. However, many of the most common sleep-linked disorders cannot yet be adequately treated.

57.11.1 Motor Control and Sleep Disorders

Among a variety of disorders that affect normal physiologic function during sleep, state-related disorders of movement frequently play a role. Periodic twitches of the

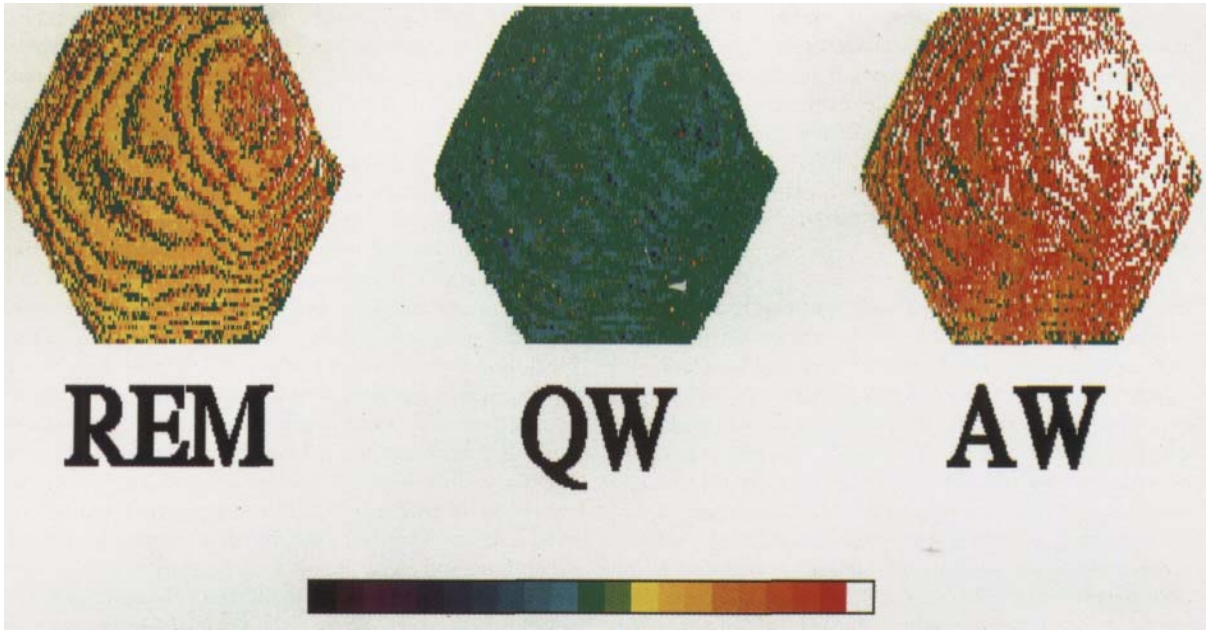

Fig. 57.4. Optical reflectance images representing activity changes over 1.6mm areas of the dorsal hippocampus during rapid eye movement sleep *(REM),* quiet waking *(QW),* and active waking *(AW),* subtracted from images collected during quiet sleep (QS). The images illustrate overall changes in activation of large numbers of neurons, as well a regionalized activity. Pixel-by-pixel differences between the state shown and QS are displayed and were significant at a < 0.05. The *color bar* represents the pseudocolor scale indicating activity changes. *Yellow to red pixels* indicate areas of increased activity (decreased reflectance), with *white* representing an activity increase of 3.3%. *Blue to purple pixels* indicate areas of decreased activity (increased reflectance), with *black* representing an activity decrease of 3.3%. *Green pixels* indicate no significant difference in activity between the two states. Patterns of near-circles, especially apparent in REM and AW states, and parallel bands, prominent in the QW state, suggest organized regions of activation and inactivation.

limbs, especially the legs, can occur with such intensity that patients undergo momentary arousals every few seconds; such phenomena, termed nocturnal myoclonus, can contribute in a major way to insomnia (see below). Rhythmic movements in other muscle groups can occur during sleep, such as synchronous movements of muscles associated with the mandible (bruxism); such synchronous activity can result in severe dental problems. The loss of muscle tone associated with REM sleep contributes in a major way to obstructive sleep apnea and to cataplexy, a major symptom of narcolepsy.

57.11.2 Apnea

Obstructive sleep apnea is the most common cause of daytime sleepiness. The reduction in upper airway muscle tone that accompanies sleep, and especially the loss of tone that is characteristic of REM sleep, underlies the mechanism for obstructive apnea, since a condition is created in which air must move through a flaccid passage as negative pressure is sustained by a still-active diaphragm. The loss of muscle tone occurs in normal individuals, causing narrowing of the airway and the characteristic breathing noises of sleep as flaccid tissue vibrates with air movement through a restricted airway. However, in certain individuals with anatomically small airways, sleep-induced reduction of muscle tone constricts airway size further as the tongue recedes; constriction of the air passages increases air speed and reduces pressure (Bernoulli effect) as the diaphragm descends, causing the pharyngeal walls to be "sucked" together, blocking inspiration.

Cessation of airflow does not immediately arouse the patient. Instead, inspiratory effort continues to be exerted against the closed airway as oxygen levels in tissue decrease below normal levels. The apnea is terminated by a brief arousal, which restores muscle tone, opens the airway and allows an incoming rush of air, which is usually accompanied by a snort. The apnea process resumes within seconds as the individual returns to sleep [106]. The patient is unaware of this process, although the bed partner can scarcely be oblivious to it. Interrupted sleep of this kind does not have the restorative properties of continuous sleep [8]. Therefore, even though the sleep apnea patient may get 8 or 9 h of sleep a night, he (the disease is more common in men then women) awakes exhausted. Moreover, catecholamine release associated with the apnea-induced hypoxia, and the considerable venous return associated with sustained negative thoracic pressure from prolonged inspiratory efforts, has the potential for serious cardiovascular consequences. Obstructive sleep apnea can seriously exacerbate other cardiac pathologies, such as congestive heart failure.

An effective, though somewhat cumbersome, treatment for obstructive sleep apnea is CPAP (continuous positive airway pressure). The patient wears a mask over his nose while he sleeps. Positive pressure exerted by air pumped through the mask "splints" the airway open even as the individual sleeps. Sleep is no longer interrupted, and a remarkable and immediate restoration of waking alertness occurs after even a single night's sleep with CPAP [106]. Other therapeutic approaches include mechanical splints to maintain an extended head position (neck braces), prostheses to maintain a forward thrust of the mandible and attached tongue, and surgical resection of excess oropharyngeal tissue. The last approach is especially effective in children, in whom hypertrophied tonsillar tissue may lead to diminished airway size and increased airway resistance.

Obstructive sleep apnea implies that diaphragmatic effort continues while the upper airway is blocked. However, certain brainstem or high cervical cord surgeries or lesions can elicit a failure of automatic ventilation during sleep. This condition is associated with a failure of phasic activation of both the diaphragm and other respiratory muscles. The condition is often treated with implanted diaphragmatic pacemakers, a technique that has to be applied with considerable care, since too vigorous activation of the diaphragm can elicit the Bernoulli effect and induce obstructive apnea.

57.11.3 Developmental Issues

We have noted the marked effect of sleep on the respiratory musculature and on central processing of respiratory patterning, and the potential for sleep to modify sensory processing in the adult. These state influences pose special problems for normal physiologic control during development. To give one example, the loss of muscle tone in respiratory muscles creates special challenges for infants during REM. Infants have compliant thoracic walls as the rigidity later imposed by a cartilaginous rib cage is lacking. If compliance increases even further owing to a loss of thoracic wall muscle tone during REM, this allows the rib cage to collapse easily during inspiratory efforts during REM sleep, creating potentially dangerous low levels of oxygen reserve [42]. A few development-related syndromes have specific dependences on sleep states, and are described below.

Congenital Central Hypoventilation Syndrome. A failure of automatic ventilation that manifests itself shortly after birth is termed congenital central hypoventilation syndrome (CCHS); it is often called "Ondine's curse," a term derived from a Greek myth but coined for an adult syndrome induced by high cervical lesion [91]. Infants with this uncommon syndrome exhibit normal peripheral chemoreceptor function [31] and show increases in ventilation in response to metabolic demands, e.g., in exercise, but cease breathing during quiescent states or on entry into sleep. They must be mechanically ventilated at night, and metabolic requirements must be carefully titrated during periods of special demands, such as sleeping periods during other illnesses.

Sudden Infant Death Syndrome. A leading cause of infant death in a number of western countries is the sudden infant death syndrome (SIDS). Infants are found dead, typically following a period in which they should have been sleeping, and no outstanding mechanism for death is revealed at autopsy. In the United States, the syndrome occurs in 2.5/1000 births, and thus results in 5000-6000 deaths a year. The age for death shows a marked prominence at 2-4 months, with few newborns or older infants succumbing to the syndrome. A prone sleeping position has been implicated as one (but not the only) factor in several countries. A high incidence of petechiae in the upper airway following death has been suggested as indicative of upper airway obstruction during the terminal stages. Infants who later succumb to the syndrome show a number of aberrations in state organization, cardiac rate variation, and respiratory variability (fewer short apneas) from a very early age. Siblings of SIDS infants, who are at elevated risk for the syndrome, also show disturbed physiologic signs from the first few days of life, suggesting that the mechanisms underlying SIDS have their origins in fetal life [37,38].

Rett's Syndrome. A syndrome exists in which there is disturbed respiratory patterning during waking, and normalization of breathing during sleep. The syndrome, Rett's syndrome, is an X-chromosomal dominant mutation that leads to arrested development, mental retardation, stereotyped hand movements, cortical atrophy and extrapyramidal dysfunction in females, and is associated with severe behavioral dyscontrol of an affective nature. Breathing during waking is frequently tachypneic, interspersed with apneic episodes; this patterning is immediately stabilized on entry into sleep, suggesting a rostral brain origin for aspects of breathing control in the syndrome [61].

Sleep Walking. Sleep walking typically occurs during non-REM sleep in children, and often disappears with aging. Night terrors, which consist of terrifying, poorly recalled dreams and nocturnal enuresis, occur in non-REM sleep as well [25]. In most cases, these parasomnias pose no problem for the patient (provided the environment is safe for sleep walkers) and disappear with development.

57.11.4 Narcolepsy

Narcolepsy is defined by four symptoms. A primary sign is excessive daytime sleepiness. Regardless of how many hours the narcoleptic sleeps, he or she is as sleepy as a normal individual would be after several nights of missed sleep. Naps produce a temporary relief from sleepiness, but sleepiness returns within an hour or two. Narcoleptics also experience problems with motor control. Sudden emotions, including anger, laughter, sexual arousal and other

situations that may be idiosyncratic to the individual, cause a loss of muscle tone called cataplexy, which may result in the individual falling to the ground. A related symptom is "sleep paralysis," a loss of muscle tone at sleep onset or awakening. Although awake, the individual is unable to move, in some cases for several minutes. Many narcoleptics also experience hypnagogic hallucinations. These are hallucinations at sleep onset, with features of the environment becoming incorporated into a dream narrative.

One hypothesis explains the symptoms by suggesting that narcolepsy is a disease in which REM sleep components become dissociated from each other [78]. Cataplexy can be seen as the atonia of REM sleep being inappropriately triggered by emotions. Sleep paralysis can likewise be seen as an inappropriate triggering of the REM sleep atonia mechanism. Evidence supporting this hypothesis at a neuronal level has been obtained from recordings of brainstem activity in narcoleptic dogs. Cells that were normally selectively active only during the atonia of REM sleep became active prior to and during cataplexy [98,99]. The hypnagogic hallucinations of narcolepsy can be seen as dream imagery intruding into waking. The sleepiness of narcolepsy is somewhat harder to incorporate into this hypothesis, but may represent a release of somnogenic mechanisms normally linked to REM sleep. Narcolepsy is linked to a particular HLA (human leukocyte antigen) genetic marker [44]. This marker, while present in 20% of the normal population, is present in approximately 95% of narcoleptics (this percentage varies somewhat in different ethnic groups). Because of the linkage of HLA markers to certain autoimmune diseases, it has been hypothesized that autoimmune processes are involved in damaging the brain and thereby produce narcolepsy. However, research to date has not identified CNS damage or evidence of autoimmune activity in narcoleptic humans or dogs.

The standard treatment for narcolepsy is to administer stimulants, such as Ritalin, as needed. However customary doses of stimulants do not restore alertness to normal levels, and higher doses taken throughout the day have unacceptable side effects including the development of tolerance. Narcolepsy typically begins in adolescence and is a lifelong illness [35].

57.11.5 REM Behavior Disorder

Another disorder of REM sleep mechanisms is the REM sleep behavior disorder. In this disorder, the patient acts out dream mentation, often injuring himself or his bed partner [90]. An imbalance between the motor excitation of REM sleep and the protective peripheral motoneuron hyperpolarization appears to be implicated in this disease. Treatment with clonazepam, which appears to dampen the excessive motor activity and the accompanying overly active dreams of these patients, is an effective treatment. However, some of the abnormalities of motor tone activation during REM sleep persist after treatment and can be seen in the electrical recordings of muscle activity. Recent work indicates that many narcoleptics also have REM sleep behavior disorder [89], implicating an underlying breakdown in REM sleep regulation in both diseases.

57.11.6 Insomnia

Insomnia, a difficulty in initiating or maintaining sleep, is the most common and the most poorly understood sleep disorder. Insomnia does not manifest any single set of symptoms, but may result from multiple causes, and the etiology is unknown for many afflicted patients. One source of insomnia results from exaggerated periodic peripheral limb movements during sleep, which can result in repeated arousals that interfere with a night's rest. A major source of insomnia complaints results from conditioning of stimuli during bedtime that normally should be associated with waking behavior. Resentment toward a bed partner, heightened intellectual activity induced by working on projects in bed shortly before trying to sleep, or other conditioned behaviors that affect mental activity adversely for entering a sleep state can result in difficulty in initiating sleep. Patients afflicted with such negative conditioning often sleep well when removed from the situation and placed in a neutral environment, such as a hotel room or sleep laboratory. Overuse or late-in-the-day use of caffeinated beverages often plays an unrealized role. Irregular sleep onset and waking times can disturb normal circadian rhythms (cf. Chap. 58).

A small proportion of insomniac patients exhibit uncontrolled misalignment of circadian rhythms [82]. Stable circadian rhythms time-locked to a particular time of rising can more readily be established by regular times of awakenings, and by time-locked exposure to relatively bright light [14,15]. The latter light treatment also shows promise for alleviating symptoms associated with seasonal affective depression, a syndrome accompanied by pathologic early morning rising.

Transient insomnia can be effectively treated with benzodiazepine hypnotics [83]. While early work had suggested that these agents worked through GABAergic mechanisms, recent work indicates that a non-GABAergic mechanism may be involved [67]. Long-term treatment with hypnotics is not indicated for chronic insomnia. For disturbances of circadian rhythm and particular behavioral issues, behavioral treatments, such as helping the patient regularize bedtime and eliminate daytime naps are effective in chronic insomnia. Psychotherapy may help some patients. Motor disorders that disturb sleep can be treated pharmacologically. However, successful treatment for many cases of insomnia remains elusive. The science of sleep disorders medicine did not exist 25 years ago. Disease entities are only now being defined and subdivided. Epidemiological studies indicate that more that 20% of the population have serious sleep disorders that interfere with waking function [101]. Obviously much more remains to be done. Future clinical advances are heavily dependent on basic work that is beginning to reveal

how the states are generated. The key to both basic and clinical advances is achievement of some insight into the function of sleep, which, however, continues to challenge sleep researchers.

57.12 Conclusions

At the biochemical level, the functions of sleep remain obscure. A further mystery is whether REM and non-REM sleep have distinct roles. At the behavioral level, it is clear that sleep loss causes degradation of performance and, at least in rats, can cause death. A major challenge for the future is to harness molecular biological techniques to elucidate the mystery of the function of sleep and explain the well-known consequences of sleep loss (it makes you tired!) at a molecular level.

Sleep pathologies are associated with high levels of morbidity. Even in the absence of a functional understanding of the underlying pathologies, considerable progress has been made at devising effective treatments. However, narcolepsy and insomnia remain intractable problems for the clinician. There is little doubt that truly effective treatments will require a better understanding of the homeostatic dynamics of the sleep process. The same is also true for hypersomnia syndromes, the sudden infant death syndrome and sleep-related modulation of the severity of a number of other diseases.

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